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PAPER NO. 21

PERCUTANEOUS ABSORPTION OF CHEMICAL VAPORS

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INTRODUCTION

Some military and industrial chemical vapor exposure situations require determination of the hazard involved in skin exposures even when respiratory protection is provided. Yet, we have very little information about the penetration of vapors and gases through the skin. For example, hydrazine, an important propellant, is used in aircraft emergency power units, the Space Transportation System, and satellite systems. Hydrazine fuels have been identified as suspect carcinogens, and human exposure limits have been set at very low levels. Protection from hydrazine vapor inhalation and liquid hydrazine contact is essential to the long term health of military and civilian workers. However, rates of penetration of hydrazine vapor through the skin have not been quantitated. As a precaution against skin absorption, the Air Force requires use of the bulky Self-contained Atmospheric Ensemble (SCAPE) to protect against accidental exposure to hydrazine vapors. In other occupations individuals are required to work in areas where there are high vapor concentrations of materials such as jet fuels. In these and many similar situations, quantitation of vapor penetration through unprotected skin would aid in determining whether full suit protection is necessary or whether other protective measures might be sufficient.

Limited studies of penetration of vapors in human volunteers (Riihimaki and Pfaffli, 1978) and primates (Hafner et al., 1975) have been published. Because of the moral and legal problems inherent with human studies, we wanted to develop a method for whole-body vapor exposure with respiratory protection in a more practical species, the laboratory rat. With this methodology, we and other individuals could investigate dermal vapor penetration of a wide variety of important chemicals. Dihalomethanes were

chosen as the initial chemicals to investigate vapor penetration because they were expected to penetrate the skin well, are easily detected in blood, and are metabolized in known pathways. (Gargas and Andersen, 1982).

METHODS

Rats were trained to wear a latex mask and harness (Figure 1) for at least 3 eight hour periods prior to the exposure. On the day prior to exposure we anesthetized the rats with a Ketamine/Xylazine mixture (70/6 mg per kg body weight), closely clipped the rat's fur and implanted a jugular cannula which was advanced toward the heart to sample mixed venous blood during the dermal vapor exposure.

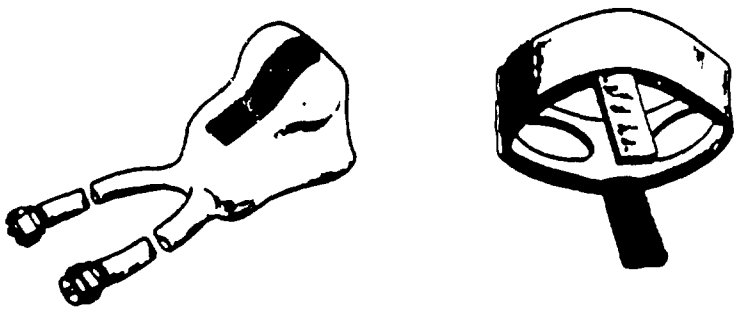

Figure 1. Harness and mask used to supply the rats with uncontaminated breathing air during the whole-body vapor exposure.

On the day of the exposure, six unanesthetized rats were exposed to carefully controlled vapor concentrations in a specifically designed chamber (Figure 2), while being provided positive pressure breathing air through the mask. Fabrication of the harnesses and masks and operation of the chamber have been previously described (McDougal et al., 1985). Blood samples were drawn from the jugular cannula just prior to and during the exposure. Dihalomethane concentrations in 0.1 mL blood were determined using gas chromatography with electron capture detection after extraction with 1 mL hexane (for dibromomethane) or 1 mL heptane (for bromochloromethane).

The amount of dihalomethane vapor which penetrated the exposed skin surface of the rat was calculated from the blood concentrations using kinetic calculations based on physiological modeling concepts. Dihalomethane which penetrated the skin had to be either metabolized, exhaled, stored in blood or stored in tissues (Figure 3).

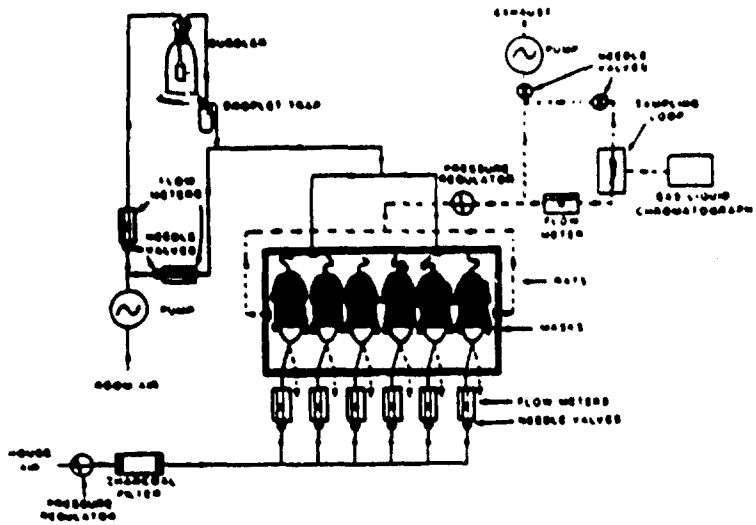

Figure 2. Schematic of the contaminant generation and monitoring apparatus and the dermal vapor absorption chamber. From McDougal et al. (1985) with permission.

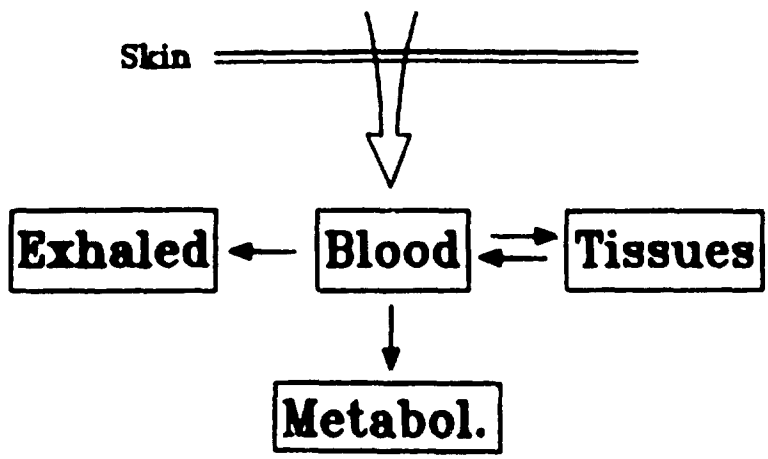

Figure 3. Disposition of the parent chemical which penetrates the skin according to a simplified kinetic model. See text for details.

The total amount metabolized during the four hour exposure was determined from plasma bromide concentrations at the end of the exposure by the method of Gargas and Andersen (1982). This was possible because each model of dihalomethane metabolized produced either one (bromochloromethane) or two (dibromomethane) moles of bromide and the half-life of bromide is 2.8 days. The total

dihalomethane exhaled during the exposure can be calculated from the area under the blood concentration curves, the ventilation rate, and the blood/air partition coefficient. The total amount stored in the blood at the end of the exposure can be calculated from the blood volume of a rat and the blood concentrations. Total amount stored in tissues at the end of the exposure can be calculated from the blood concentrations and the tissue/blood partition coefficients (see McDougal et al., 1985 for details).

RESULTS

Figure 4 shows blood concentrations from individual rats during a representative exposure to 40,000 ppm bromochloromethane. At this exposure the blood concentrations rose rapidly but were almost at a plateau by 2 hours. The small variability in blood concentrations suggests that the masks did not leak, since even a slight opportunity for inhalation of such a high concentration of vapor would produce a marked change in blood concentration.

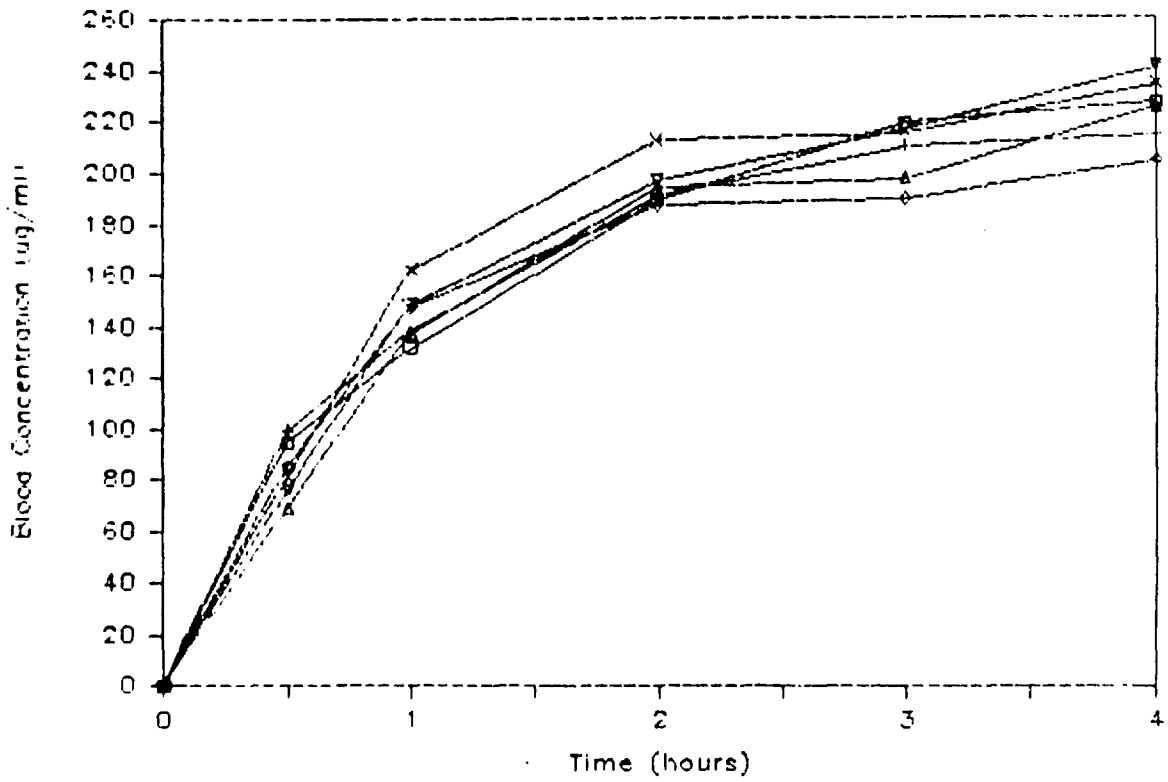

Figure 4. Blood concentrations of bromochloromethane during a 4 hour whole-body vapor exposure to 40,000 ppm bromochloromethane. Each line represents an individual rat.

Table 1 summarizes the disposition of the dibromomethane vapor which penetrated at each of four exposure concentrations. This shows that total dibromomethane absorbed is directly related to exposure concentration but that the amounts exhaled and metabolized are not directly related to exposure concentration. Table 2 summarizes the same information for bromochloromethane, with essentially the same relationships as dibromomethane.

TABLE 1. FATE OF DIBROMOMETHANE AFTER FOUR EXPOSURE CONCENTRATIONS

Exposure Conc. (ppm)	Blood Conc. (ug/mL)	milligrams of DBM				Total absorbed (mg)
		Tissue	Blood	Exhaled	Metabol.	
500	1.3	0.3	0.01	0.3	3.3	3.9
1,000	4.8	1.3	0.1	0.9	6.8	9.0
5,000	45.8	11.9	0.5	7.1	17.9	37.4
10,000	144.7	46.7	1.9	26.5	21.2	96.3

The amount of dibromomethane which was stored or exhaled was calculated from blood concentrations. The amount metabolized was determined from plasma bromide concentrations.

TABLE 2. FATE OF BROMOCHLOROMETHANE AFTER FOUR EXPOSURE CONCENTRATIONS

Exposure Conc. (ppm)	Blood Conc. (ug/mL)	milligrams of BCM				Total Absorbed (mg)
		Tissue	Blood	Exhaled	Metabol.	
2,500	6.2	1.1	0.1	2.6	9.3	13.1
5,000	26.0	4.0	0.2	8.9	11.5	24.7
20,000	104.4	16.1	1.0	32.6	20.6	70.3
40,000	224.4	37.9	2.3	77.5	37.0	155.6

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DISCUSSION

Achieved blood concentrations of dibromomethane after an inhalation exposure to 200 ppm dibromomethane are about 13 to 15 micrograms/mL. This blood level would be achieved with a whole-body vapor exposure of about 3,000 ppm. This suggests that the chemical in the blood in this study is not due to inhalation. If the rats were receiving their dose via leaks in the masks, there would be a much greater variability than found here (Figure 4).

We think of the skin as a barrier to the penetration of chemicals and it certainly provides better protection than the mucous membranes and the lungs. However, due to the large surface area available for absorption, it appears that the skin can be a significant route of entry for vapors. In fact, in this study dihalomethanes penetrated the skin well enough to saturate metabolic processes. Saturation is indicated by the non-linear increases in achieved blood concentration with increasing exposure concentration (Figure 5).

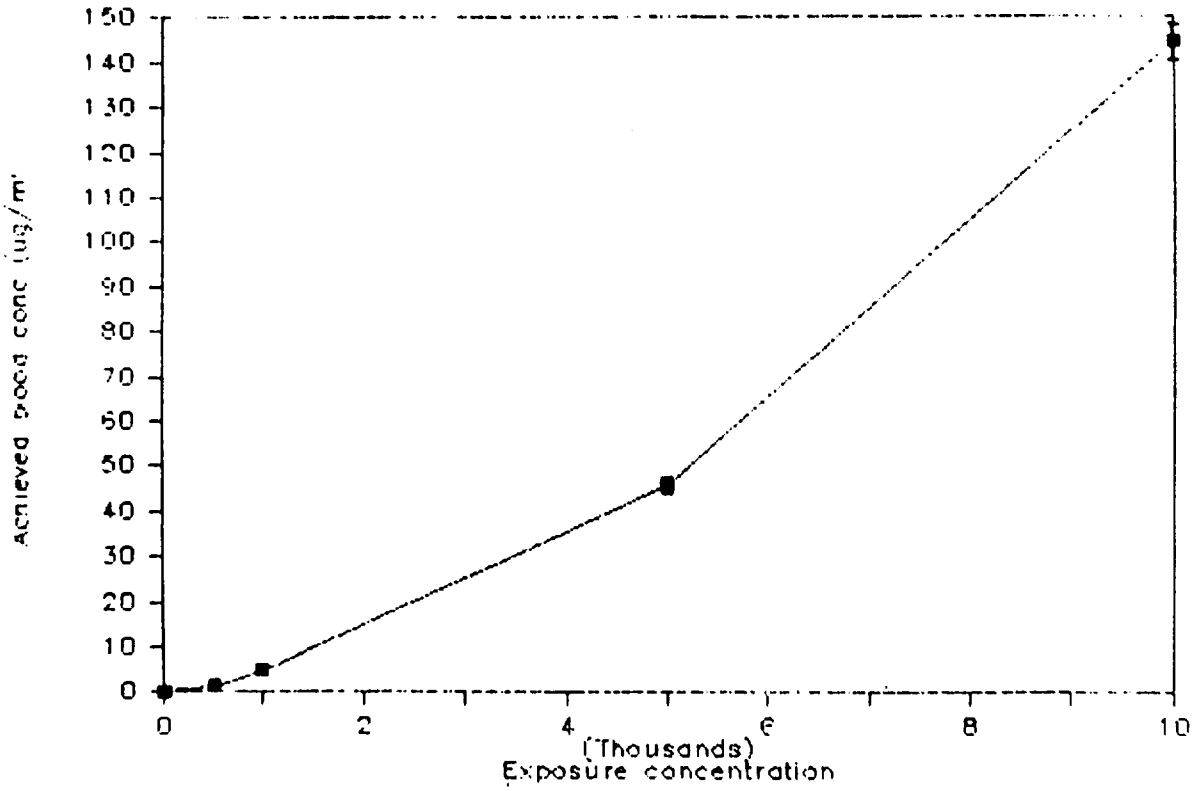

Figure 5. Relationship between achieved blood concentration and whole-body vapor exposure concentration for dibromomethane.

Figure 5 also illustrates the importance of some type of kinetic modeling in the interpretation of in vivo penetration studies. The rate of penetration of a chemical through the skin should be constant during an exposure and according to Fick's law, the rate should be proportional to the exposure concentration as shown in this study. However, elimination of most chemicals by metabolism is saturable, and without understanding these processes, determination of rates of penetration will give widely variable numbers. Blood levels alone from in vivo exposures would give very different estimates of permeability depending on whether or not metabolism was saturated at that exposure concentration. This is illustrated in another way by Figure 6. These bar graphs compare the disposition of dibromomethane at the highest and lowest exposure concentrations used in this study.

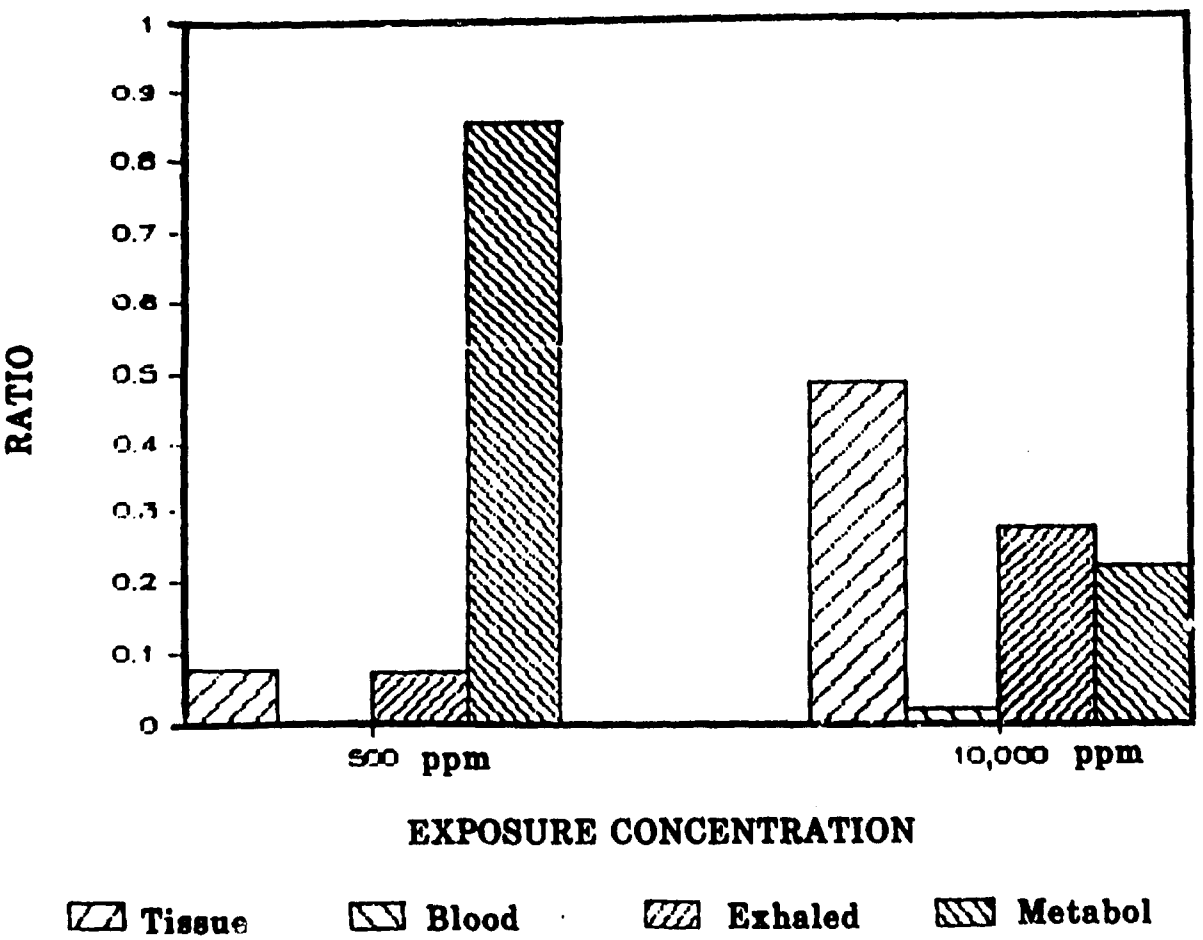

Figure 6. Bar graphs which represent the ratio of the amount of parent chemical which has been stored and metabolized or exhaled during two whole-body vapor exposure concentrations.

After a four hour exposure to 500 ppm, 85% of the parent which has penetrated the skin is metabolized and exhalation and tissue storage make up less than 10% each. After four hours of exposure to 10,000 ppm, only 22% of the parent has been metabolized. At this higher concentration, the majority of the parent is stored in tissues (49%) and a significant amount has been exhaled (28%). Similar exposure concentration differences in disposition were found with bromochloromethane and would be found with other lipophilic chemicals which exhibit saturable metabolism. This illustrates very dramatically the need for understanding the pharmacokinetics of a chemical during in vivo penetration studies if we wish to estimate meaningful absorption rates.

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